

## CORONARY ARTERY DISEASE PREVENTION &amp; THERAPY UPDATE

## Is There an Obesity Paradox?

Athanasios Triantafyllou, MD, FESC

Department of Cardiology,  
Evangelismos Hospital, Athens, Greece

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*mellitus*

## ABBREVIATIONS

BMI = body mass index  
CABG = coronary artery bypass grafting  
CHD = coronary heart disease  
CRET = cardiac rehabilitation and  
exercise training  
CVD = cardiovascular disease  
HF = heart failure  
HTN = hypertension  
NSTEMI = non-ST elevation myocardial  
infarction  
PCI = percutaneous coronary intervention

Correspondence to:  
Athanasios Triantafyllou, MD, FESC  
E-mail: [atriantaf1@yahoo.gr](mailto:atriantaf1@yahoo.gr)

## INTRODUCTION

Obese people have excess body fat. Overweight people have excess weight (weight includes bone, fat and muscle). Currently overweight and obesity are defined by body mass index (BMI: weight in Kg/height in meters squared, kg/m<sup>2</sup>). In adults, *overweight* is defined as a BMI of 25-29.9 kg/m<sup>2</sup>; *obesity* is defined as a BMI >30 kg/m<sup>2</sup>. Other less commonly used indices, but possibly with more predictive power, include waist circumference, waste-to-hip ratio, weight-to-height ratio and body fat.<sup>1</sup>

Obesity is a highly prevalent metabolic disorder that is increasing in epidemic proportions in both children and adults in the United States<sup>2</sup> and the European countries as well. Obesity is associated with numerous comorbidities, such as dyslipidemia, hypertension, reduced insulin sensitivity, diabetes mellitus, left ventricular hypertrophy, certain cancers and sleep apnea disorder.<sup>3-6</sup> Obesity is also an independent risk factor for cardiovascular disease (CVD), including hypertension (HTN), coronary heart disease (CHD), and heart failure (HF) and is associated with an increased risk of morbidity and mortality.<sup>7-9</sup>

However recent studies have shown that obese people with chronic diseases have a better chance of survival than normal-weight individuals do. This finding has been called **obesity paradox**.<sup>10,11</sup> The obesity paradox refers to the fact that sometimes being heavier -even being overweight or slightly obese- is associated with lower, rather than higher, death rates. Severe obesity is consistently, uncontroversially and unparadoxically bad for one's health, and thus it is not going to be part of this discussion.<sup>12</sup>

**'OBESITY PARADOX' AND CARDIOVASCULAR RISK  
(POPULATIONS WITH HEART FAILURE, CORONARY  
HEART DISEASE AND HYPERTENSION)**

Although obesity via its negative impact on systolic and diastolic function predisposes to overt heart failure (HF), clinical evidence suggests that overweight/obese patients with HF paradoxically seem to have a better clinical prognosis than do their lean counterparts with clinical HF. Thereafter obesity is a risk factor for developing HF (Figure 1), but after the onset of HF, obesity is a positive predictor for survival.<sup>13-15</sup> The existence of this obesity paradox has led physicians to question whether obesity should be treated when associated with HF.

Horwich et al<sup>41</sup> studied 1,203 individuals with New York Association class IV HF and found that higher BMI was associated with better survival (Figure 2) and multivariate analysis showed an inverse association between BMI and mortality.

This phenomenon of obesity paradox is also well described in populations with coronary heart disease (CHD) and hypertension (HTN).<sup>16,17</sup> Despite the negative

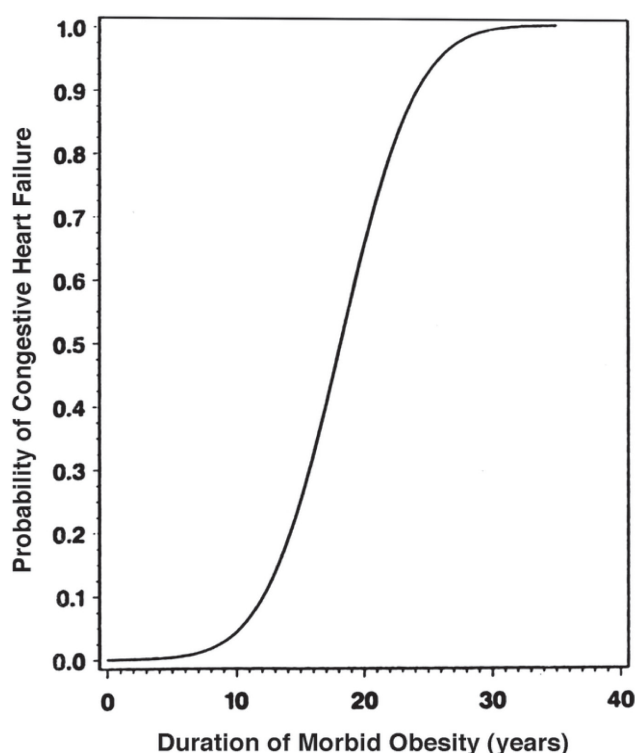


FIGURE 1. Sigma curve showing the probability of heart failure as a function of duration of morbid obesity. (Reproduced with permission from Alpert MA, Terry BE, Mulekar M, et al. *Am J Cardiol* 1997; 80:736-740.

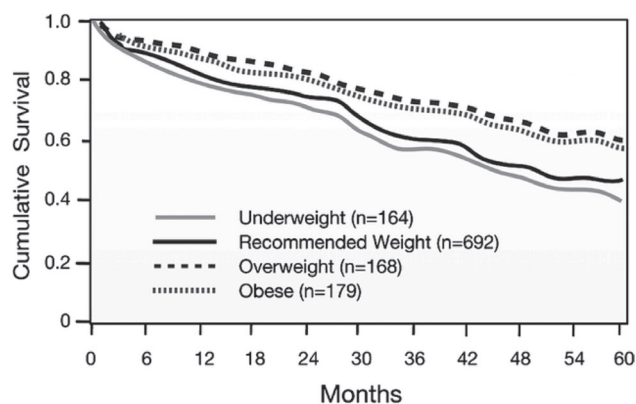


FIGURE 2. Risk-adjusted survival curves for the 4 body mass index categories at 5 years in a study of 1,203 individuals with moderate to severe heart failure. Survival was significantly better in the overweight and obese categories.

association between higher BMI and CHD, many studies suggest paradoxically better prognosis in obese patients with CHD and in patients undergoing revascularization (percutaneous coronary intervention-PCI, or coronary artery bypass

grafting-CABG surgery). Recently, in a systematic review of 40 cohort studies including 250,000 patients during 3.8 years of follow up, Romero-Corral et al,<sup>17</sup> reported lower total and cardiovascular mortality in overweight and obese patients with CHD as compared to underweight and normal weight individuals. However, in patients with severe obesity (BMI of  $>35 \text{ kg/m}^2$ ), excess risk in cardiovascular mortality was noted with no increase in total mortality. These authors concluded that the lack of discriminatory power of BMI to differentiate between body fat and lean mass could have led to better clinical outcomes in overweight and obese patients.<sup>17</sup>

Another trial examining the glycoprotein IIb/IIIa inhibitor abciximab in patients with unstable angina /non-ST-segment elevation myocardial infarction (NSTEMI) who were not scheduled for coronary intervention showed increased 1-year mortality rates in lower-weight patients compared to normal-weight and obese patients (9.6% in 75-kg group compared with 7.45 and 6.6% in patients with body weight 75-90 kg and  $>90 \text{ kg}$ , respectively:  $p<.001$ ).<sup>18</sup> Buettner and colleagues,<sup>19</sup> looked at the impact of obesity in 1,676 patients with unstable angina/NSTEMI treated with an early invasive strategy. During 3 years of follow-up, there was almost a linear reduction in all-cause mortality, from 10% in patients with normal BMI to 8% in overweight patients, to 4% in obese patients, to 0% in severely obese patients with BMI  $>35 \text{ kg/m}^2$ . These findings of better prognosis in obese patients with CHD are further supported by encouraging evidence from PCI studies and large registries. Analysis of the Bypass Angioplasty Revascularization Investigation registry,<sup>20</sup> including 2,108 patients who underwent PCI and 1,526 patients who underwent CABG, revealed that every unit increase in BMI in the PCI group was associated with 6% lower risk of in-hospital events, including death, myocardial infarction, stroke, and coma. However, in the CABG group, there was no impact of BMI on early in-hospital outcomes. In contrast, higher BMI was associated with worse long-term outcomes in the CABG group but not in the PCI group.<sup>20</sup> However, patients at both extremes, underweight (BMI  $<18.5 \text{ kg/m}^2$ ) and extremely obese (BMI  $>40 \text{ kg/m}^2$ ) had significantly higher mortality and higher rates of major adverse cardiac events.<sup>21</sup>

Similarly, studies in populations with HTN have suggested better outcomes and better long-term prognosis in obese patients. These studies suggest that although obesity is a powerful risk factor for HTN and left ventricular hypertrophy, obese hypertensive patients have a better prognosis.<sup>22</sup> It has been postulated that lower systemic vascular resistance and lower plasma renin activity in obese hypertensive patients compared to leaner hypertensive patients may partly explain their improved prognosis.<sup>8</sup>

This paradoxical association of better prognosis with higher BMI was also demonstrated in a population referred for echocardiography. The impact of left ventricular (LV) geometry and obesity on mortality was assessed in 30,920

patients with preserved ejection fraction, including 11,792 obese patients as well as 19,128 non-obese patients during an average follow-up of  $3.2 \pm 1.4$  years. Although abnormal LV geometric patterns were more commonly observed in obese versus non-obese patients (49% vs. 44%,  $P < .0001$ ), all-cause mortality was considerably lower in obese compared to non-obese patients (3.9% vs. 6.5%,  $P < .0001$ ). In both obese and non-obese patients, there was a progressive increase in mortality with progressive increases in abnormal LV geometry. Although in the entire cohort higher BMI was an independent predictor of better survival, in the obese subgroup higher BMI was associated with higher mortality. We also determined the impact of these 2 variables, including LV geometry and obesity, in 8,088 elderly patients ( $>70$  years old) with preserved LV function on all-cause mortality during a 3-year follow-up. Although abnormal LV geometry progressively increased with greater obesity (57%, 59%, and 61%;  $P < .01$  for BMI  $<25$  kg/m<sup>2</sup>, BMI of 25–30 kg/m<sup>2</sup>, and BMI  $\geq 30$  kg/m<sup>2</sup>, respectively), total mortality was strongly and inversely related with BMI (BMI  $<18.5$  kg/m<sup>2</sup>, 22% mortality; BMI 18.5–25 kg/m<sup>2</sup>, 15% mortality; BMI 25–30 kg/m<sup>2</sup>, 10% mortality; BMI 30–35 kg/m<sup>2</sup>, 9% mortality; BMI  $\geq 35$  kg/m<sup>2</sup>, 8% mortality).<sup>23</sup>

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#### UNDERSTANDING THE MECHANISMS OF THE 'OBESITY PARADOX'

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The underlying mechanisms for this apparent obesity paradox remain elusive. It is postulated that lower body weight may be associated with a heightened catabolic state with increasing levels of tumor necrosis factor and other cytokines and imbalance in cortisol/dehydroepiandrosterone ratio.<sup>6–8</sup> There is evidence from several studies linking adiposity and the natriuretic peptide system; recently, reduced natriuretic peptide levels was demonstrated in obese patients with HF.<sup>24,25</sup> This explains the earlier expression of HF with less severe symptoms in the presence of obesity secondary to reduced circulating natriuretic peptide levels. Therefore, obese patients with HF with earlier presentation and less severe symptoms receive more aggressive therapy early on, with better long-term prognosis.<sup>24,25</sup>

Other lines of evidence suggest enhanced protection against endotoxin/inflammatory cytokines with obesity as well as increased nutritional and metabolic reserves.<sup>26,27</sup> Evidence from basic science studies suggests that adipose tissue is occupied with dense soluble tumor necrosis factor  $\alpha$  receptors, which have a neutralizing effect on cytokines, including interleukin 1 and tumor necrosis factor  $\alpha$ , and might have a protective role in obese patients with acute or chronic HF.<sup>28</sup> Also, just being obese with good nutritional and metabolic reserves might confer favorable prognosis in both obese patients with HF and CHD alike. Obese patients with HF have lower baseline levels of the renin-angiotensin system, which

might protect the cardiovascular system from their deleterious effects.<sup>29,30</sup> Because obese patients have higher blood pressure levels, they might better tolerate cardioprotective medications and have a better prognosis.<sup>26</sup> Nevertheless, despite these potential mechanisms, the exact reasons for these puzzling results remain elusive. In addition, most of these studies have focused on BMI and a few on percentage of body fat, and there is little information regarding other parameters (eg, waist circumference, waist-to-hip ratio) in the obesity paradox.<sup>6</sup> Finally, many of the studies did not adjust for smoking and chronic obstructive pulmonary disease among underweight and leaner subjects, as well as nonpurposeful weight loss in the participants, which may suggest worse prognosis for almost every potential etiology.<sup>31</sup>

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#### WEIGHT LOSS

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Studies looking at the impact of weight reduction in overweight and obese cardiac patients have been controversial, some suggesting better clinical outcomes, whereas others indicating no benefits and, in fact, some studies have even suggested detrimental effects. However, other studies assessing mortality based on lean body mass and total body fat content as opposed to BMI showed that losing body fat rather than lean mass has mortality benefits.<sup>6</sup> In a study of 74 morbidly obese patients, Alpert et al,<sup>32</sup> showed that significant weight reduction  $>30\%$  of total body weight with gastroplasty (12 of 14 morbidly obese patients achieved this weight loss) resulted in improvement of New York Heart Association functional class by an average of  $>1$ . In this study, weight loss was also associated with marked improvements in left ventricular dimensions and systolic function. Mac Mahon et al,<sup>33</sup> demonstrated that even minimal weight loss of 8 kg or 17.6 lb in mildly obese subjects with HTN was associated with significantly greater reductions in left ventricular mass and wall thickness compared to reductions achieved in subjects treated with pharmacologic therapy with  $\beta$ -blockers. Among various nonpharmacologic means of weight reduction, cardiac rehabilitation and exercise training (CRET) is the most extensively studied method. In one particular study (from the Ochsner Clinic Foundation) with patients with metabolic syndrome, CRET led to a 37% reduction in the prevalence of metabolic syndrome.<sup>34</sup> In a small subgroup of 45 obese patients with CHD from the CRET program, it was demonstrated that even small reductions in body weight ( $>5\%$  or more; average, 10%) were associated with marked improvements in obesity indices, lipids, and exercise capacity when compared to the cohort that did not lose weight.<sup>35</sup> Recently, marked reductions in C-reactive protein levels were noted in obese patients with CHD following CRET, whereas lean patients had nonsignificant reductions in C-reactive protein.<sup>36</sup> In a preliminary analysis of a much larger sample size, marked improvements were noted in CHD risk factors, including C-

reactive protein, lipids, and glucose, among patients with CHD who lost weight; this group had a trend for lower mortality.<sup>16</sup> Therefore, these data do not indicate that obesity should be ignored as a risk factor just because an obesity paradox exists. In fact, obesity remains a powerful risk factor for the development of HTN, HF, and CHD, and it is believed that purposeful weight reduction should still be emphasized, particularly for the more obese patients with HTN, HF, and CHD, despite the obesity paradox. Additionally, marked weight loss with bariatric surgery has resulted in improved mortality risk, mostly related to diabetes mellitus, cancers, and CVD events.<sup>37-40</sup> Although data are limited on the efficacy and safety of these procedures in patients with established CVD, a recent study in 12 patients with severe HF<sup>41</sup> suggests safety and improvements in HF prognosis following this surgery that may be considered to be high risk in patients with HF.

On the other hand, a most recent study, which was published online (16/1/2014, *Am J Public Health*), found that obesity was associated with at least a 20% increased risk of death from all causes or from heart disease. Overall, obese adults died 3.7 years earlier from all causes and 1.7 years earlier from heart disease compared with normal-weight adults. In the study researchers said: The authors suggest that “Given the prevalence of obesity among children and young adults, early intervention is absolutely essential in order to prevent this trend from increasing exponentially as these populations continue to age”.

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## OBESITY AND DIABETES

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Recent studies suggesting that heavier people with diabetes have lower death rates than normal weight patients may be a myth! A strong body of research shows that being overweight or obese puts people at risk for chronic conditions like heart disease, diabetes, cancer and even early death. But several small studies connecting obesity to a protective effect against type 2 diabetes-related death have raised questions about a possible ‘obesity paradox,’ and whether weight can be a benefit in preventing progression of the disease.

A 2012 study published in *JAMA*, for example, studied 2,625 people recently diagnosed with type 2 diabetes, of whom only 12% had normal weight. But the larger people with diabetes lived longer than their thinner peers. Why the heavier people lived longer was not clear; the researchers speculated that genetics, or the type of fat that certain obese people accumulated compared to normal weight individuals could be responsible.

However, in a new study published in the *New England Journal of Medicine*, scientists say that this is unlikely. “We didn’t see this protective effect at all,” the study’s leader, Diedre Tobias of the Harvard School of Public Health, told: “The lowest risk was seen in the normal-weight category.”

Tobias and her colleagues looked at 11,427 female nurses and male health professionals who were diagnosed with diabetes. They were divided into groups based on their BMI, with those with a BMI over 25 considered overweight and people with a BMI over 30 considered obese. After 15 years, the scientists recorded the participants’ death rates and found that those with BMI in the 22.5 to 25 range, considered normal weight, had the lowest risk of diabetes-related death.

However, whereas ‘overweight’ implies increased risk, it is in fact associated with decreased mortality risk compared with normal weight.<sup>42</sup> Another paradox concerns the observation that when fitness is taken into account, the mortality risk associated with obesity is offset. The final paradox under consideration is the presence of a sizeable subset of obese individuals who are otherwise healthy. Consequently, a large segment of the overweight and obese population is not at increased risk for premature death. It appears therefore that low cardiorespiratory fitness and inactivity are a greater health threat than obesity, suggesting that more emphasis should be placed on increasing leisure time physical activity and cardiorespiratory fitness as the main strategy for reducing mortality risk in the broad population of overweight and obese adults.<sup>43</sup>

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## CONCLUSIONS

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Obesity is independently associated with the incidence of new CHD cases and adversely affects conventional CHD risk factors, including HTN, diabetes mellitus, dyslipidemia, and the metabolic syndrome. This negative relationship became more evident as accumulated evidence from long-term follow-up studies found that obesity was associated with CHD, independent of other cardiovascular risk factors. Data from the Pathobiological Determinants of Atherosclerosis in Youth study suggest that overweight and obesity in young adults accelerate the progression of atherosclerosis decades before the appearance of clinical manifestations. Prospective studies that reported follow-up data for more than 2 decades, such as the Manitoba Study, the Framingham Heart Study, and the Harvard School of Public Health Nurses Study, have documented that obesity is an independent predictor of clinical CHD.

Although obesity is a risk factor for the pathogenesis and progression of CVD, evidence reports the existence of an obesity paradox, in that obese patients with established CVD appear to have a better clinical prognosis. Available evidence supports the benefits of purposeful weight reduction in curbing the obesity pandemic and associated CVD. Further research is needed to better understand the puzzling obesity paradox phenomenon, the underlying mechanisms for the phenomenon, and weight reduction strategies in various subgroups and to better define the optimal weight in these special populations of high-risk patients with and without established CVD to better manage these complicated cases.



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